GENE THERAPY ADVISORY COMMITTEE

THIRD ANNUAL REPORT

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FOREWORD

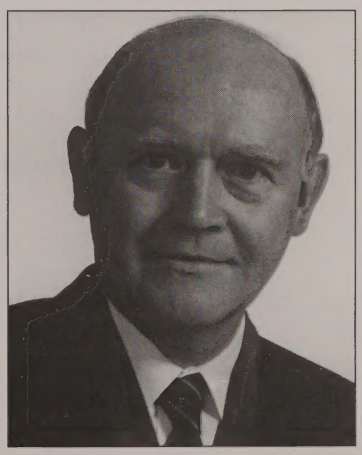
The founder chairman of the Gene Therapy Advisory Committee (GTAC), Baroness Lloyd of Highbury stood down from the Committee in 1996. I succeeded her as Chairman at the beginning of 1997. I welcome this opportunity to pay a sincere and very warm tribute to her for all that she accomplished in establishing GTAC s international renown for the quality of its ethical and scientific assessments. I am sure that all members of the Committee and the Secretariat join me in extending to her our best wishes for the future.

The second annual report from GTAC was issued in May 1996. As with the first report, it was received as an important means of ensuring that accurate information about *gene therapy* trials in the United Kingdom is placed in the public domain.

The third full year of the Committee s activity has seen four important developments. First, an increase in enquiries and submissions made to GTAC; secondly, an increase in the complexity of submitted protocols; thirdly, a continuing shift from gene therapy for single gene disorders towards strategies aimed at tumour destruction in patients with cancer; and finally, a growth in international sponsorship of UK gene therapy trials.

GTAC is mindful that it does not function in isolation and remains committed to disseminating information about UK gene therapy research to the widest audience possible. With this in mind GTAC organised its first Workshop in March 1997. A diverse audience of around 160 people was invited to attend the Workshop entitled *Gene Therapy - Myth and Reality: Hype and Practicality* . The purpose of the Workshop was to outline the achievements, the potential accomplishments and barriers to progress in gene transfer therapy. It is important that clinicians and scientists make the case for what they have achieved, for what they are doing and for their future goals in gene therapy, whilst ensuring a proper balance between the hopes and fears of society. It is my intention that the specific issues identified during the Workshop are taken forward, perhaps by consultation initiatives or in smaller follow-up workshops. A fuller report of this Workshop will appear in the Proceedings document which will be published shortly.

Finally, the Committee said farewell in 1996 to three of its founder members: Derek Crowther, Peter Lachmann and Rosemary Knights. I wish to record my thanks to these members for the substantial time and profound commitment they gave to GTAC.



Professor Norman C. Nevin
May 1997

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ANNEXES

SECTION 1 - PROTOCOLS CONSIDERED BY GTAC (1996)

1.1 GTAC met three times during 1996 and assessed a total of 11 protocols. The Committee was satisfied in principle, subject to conditions, for five protocols to proceed. The remaining six protocols are still under consideration.

1.2 Since 1993 GTAC and its predecessor, the Clothier Committee, has agreed for *gene therapy** research to proceed in human subjects for the following diseases: severe combined immunodeficiency (1), cystic fibrosis (6), *metastatic* melanoma (2), lymphoma (2), neuroblastoma (1), breast cancer (1), Hurler syndrome (mucopolysaccharidosis Type I) (1), cancer of the cervix (1), glioblastoma (1) and head and neck cancer (2).

1.3 Protocols submitted but still under review include strategies to manage acute myeloid leukaemia, breast cancer, breast cancer with liver *metastases*, glioblastoma, malignant *ascites* due to gastrointestinal cancer and ovarian cancer.

CYSTIC FIBROSIS

1.4 Cystic fibrosis (CF) was identified as a particular issue in the Science and Technology Select Committee s Third Report[1], and it has continued to have a high public and media profile. The perceived advances in CF gene therapy research and the fact that *genetic tests* for CF are the first such tests to be made commercially available directly to the public, are perhaps contributory factors to this high level of interest.

1.5 A child with CF inherits a faulty gene from each parent and CF is the most common inherited serious genetic disease in the UK. The disorder affects nearly 7,000 patients and approximately 4% of the population (over 2 million) are carriers. It has a birth prevalence of 1 in 1800 newborn. Although advances in medical management of the disease have improved the quality of life for many sufferers, the long term prognosis for almost all patients remains poor with severe lung failure usually occurring in early adulthood.

1.6 The CF gene produces a *protein* called *cystic fibrosis transmembrane conductance regulator (CFTR)*. Research groups in Europe and the US have used a variety of gene transfer approaches to ameliorate the faulty production of CFTR in CF patients. In the UK, there are currently three gene therapy groups involved in gene therapy research for CF, all of whom have employed non-viral *vectors*.

(a) Towards gene therapy for cystic fibrosis - Department of Clinical Biochemistry, John Radcliffe Hospital,/Oxford/Cambridge/ Leeds/Manchester Consortium

1.7 This is the fifth CF proposal to be considered by GTAC. It is the second protocol from the John Radcliffe Hospital based consortium to be submitted for approval.

1.8 In February 1994 GTAC approved the consortium s first trial: a single dose application nasal study of the *DNA/liposome* vector in 12 CF patients. The results* demonstrated that the procedure was well tolerated by the patients. It also provided some limited evidence of *electrophysiological* correction of the cellular defect.

1.9 Using the same vector as the single-dose study, the proposers aim to assess the safety and efficacy of multiple applications of the DNA/liposome to the nose. Patients will receive the equivalent to the highest CFTR dose found to be safe in the first single application trial. Up to 24 patients with a clinical CF diagnosis and a defined *genotype* will be recruited.

1.10 On 30 May GTAC gave conditional approval to this study, subject to minor changes to the clinical protocol and simplification of the patient information sheet.

*Because it has been necessary to use some technical terms in describing the protocols, a glossary is appendedfor these. Words appearing in the glossary are *italicised* the first time they appear in the text.

(b) Gene therapy for cystic fibrosis (CF). Delivery to nasal epithelium and lung by nebulisation of the pCF1CFTR/#67 - Royal Brompton National Heart and Lung Hospital, London.

1.11 This proposal is the second from the Brompton team investigating CFTR transfer therapy in CF patients. In the first trial the proposers investigated the CFTR *expression* following single application to nasal epithelium of a liposomal vector. A previous nasal and lung study reported in GTACs first annual report was withdrawn in favour of the current trial.

1.12 In the new trial, gene transfer will be evaluated in both the nose and the lung. Up to 16 CF adults with a known genotype and mild lung disease will be recruited. There will be two treatment groups, and a control group who will receive the liposome without the CFTR gene.

1.13 For the nose and lung study the DNA *plasmid* construct and the lipid used in liposome formulation have been altered. The original liposome vector contained a plasmid incorporating the CFTR gene with a *promoter* sequence from a *Simian Virus* and a DC-Chol/DOPE *cationic* lipid. The new lipid formulation was developed by Genzyme Corporation.

1.14 The DNA/liposome complex will be delivered to the respiratory tract by nebulisation.

1.15 In November 1996 GTAC gave conditional approval subject to changes to the patient group and an undertaking to perform follow up experiments.

HEAD AND NECK CANCER

1.16 Head and neck cancer is a common *malignancy*. It is the sixth most frequent cancer in the world. There was an estimated 378,500 new cases in 1992.

1.17 The use of tobacco and consumption of alcohol are the two most important risk factors associated with this cancer. Surgery, radiotherapy, and (in more advanced cases) chemotherapies are standard therapeutic approaches. Despite improvements in cancer *prophylaxis*, the overall 5 year survival rate for head and neck tumours remains amongst the lowest of the major cancers.

1.18 The most frequent genetic change in this cancer involves *mutations* of the p53 *tumour suppressor gene*. The normal gene codes for a nuclear protein which is thought to inhibit *tumorigenicity* by regulating cell *proliferation*. The loss of p53 function would therefore contribute to unrestrained cellular growth and malignancy. 43% of head and neck tumours involve p53 mutations.

(a) Phase I, Open-Label, Dose-Escalation Trial of Intra-Tumoral Injection with an E1B Attenuated Adenovirus ONYX-015, into Recurrent and Locally Advanced p53(-) Squamous Cell Tumours of the Head and Neck - Beatson Oncology Centre, Glasgow.

1.19 Adenoviruses are common DNA containing viruses primarily found in the respiratory tract where they can cause infections ranging from self limiting respiratory infection to fatal pneumonia. In order for the virus to infect, reproduce and *lyse* the cell it must inactivate the cell s p53 protein. The virus does this by producing a protein called E1B.

1.20 Onyx-015 is an adenovirus that has been modified so that it can no longer produce E1B. These modifications result in Onyx-015 becoming replication deficient (attenuated). In this case replication deficiency (attenuation) results in Onyx-015 being able only to reproduce, and thus lyse, p53 *mutant* or deficient cells. Both in vitro and in vivo studies have demonstrated that Onyx-015 has no *cytopathic* effects on normal human cells such as *fibroblasts* or certain types of p53 deficient human cancers.

1.21 The Onyx-015 vector is to be injected directly into the tumour of patients with recurrent head and neck tumours. The patients selected for the trial are those ineligible for curative resection of their tumour and in whom other established therapies have failed. The investigators intend to recruit between 16 and 30 patients.

1.22 In January 1996 GTAC gave conditional approval to this study, subject to clarification of the follow-up procedures.

(b) Phase I study in patients with recurrent metastatic squamous cell carcinoma of the head and neck using SCH 58500 (rAd/p53) - Royal Marsden Hospital, London

1.23 SCH 58500 is a *recombinant*, replication deficient adenoviral vector containing the human p53 gene. Experimental data from the SCH 58500 vector using p53 deficient or mutant human head and neck tumour lines indicate that restoration of p53 activity could result in the suppression of tumour growth.

1.24 This trial is part of a multi-centre study. At the Royal Marsden Hospital up to 18 adult patients with recurrent or metastatic squamous cell carcinoma and evidence of p53 mutation will be recruited. The SCH 58500 vector will be administered by a single intra-tumoural injection. Patients will be hospitalised for clinical observations, including monitoring of vector excretion for at least 72 hours.

1.25 In September 1996 GTAC gave conditional approval to a revised protocol.

GLIOBLASTOMA

1.26 Worldwide, serious *neurological* disease affects about 3% of the human population. In the UK approximately 4,000-5,000 patients with brain tumour are diagnosed each year. 50% of primary brain tumours are gliomas. The most common glioma is glioblastoma multiforme.

1.27 Current treatments for glioblastoma (radiotherapy, chemotherapy, surgery) are *palliative* and rarely alter the long term prognosis. The median survival rate for patients is approximately a year. Five year survival is extremely rare.

1.28 Herpes Simplex Virus type 1 (HSV1) is a virus associated with cold sores, genital infection and occasionally inflammation of the brain. HSV1 has a specific ability to grow in central nervous system tissue and as such is a promising vector for gene therapy in *neurological* disease.

A Phase I dose-escalation study of intra-tumoural injection with modified HSV Type 1 (ICP 34.5$^-$) into primary and recurrent malignant glioma - Department of Clinical Oncology, Beatson Oncology Centre, Western Infirmary, Glasgow.

1.29 This trial uses a modified HSV1 of the 1716 strain. HSV1 1716 only replicates in dividing *proliferative* cells such as malignant tissue. Viral replication in these cells results in their death. The mechanism by which HSV1 1716 is selectively *lytic* is not completely understood. However it is known that in HSV1 mutants that lack a specific *virulence* determinant, a protein called ICP 34.5 fails to replicate and spread in normal *neural* tissue.

1.30 In the study approved by GTAC the safety and potential efficacy of this approach will be evaluated in patients who have relapsed after conventional treatments (radiotherapy/surgery) and who are unsuitable for chemotherapy. It is anticipated that between 18 and 25 patients will be enrolled into the study. Each patient will receive a 1ml intracranial injection of HSV 1 1716 administered to the tumour by *stereotactic* localisation.

1.31 This approach to cancer treatment is not strictly gene therapy but has been submitted to GTAC, in accordance with paragraph 13 of GTAC s guidance to proposers document[2], as it uses a genetically modified organism.

1.32 The Committee gave conditional approval in December 1996 to this trial and recommended that the proposers should study the effects of the highest dose in primates.

PROTOCOLS STILL UNDER REVIEW AT THE END OF JANUARY 1997

1.33 Five proposed protocols on gene therapy research submitted to GTAC during the Committee s third year of work are still under consideration. These are:

(i) two genetic prodrug activation therapy (GPAT) or *suicide gene* approaches. The first, for newly diagnosed, previously untreated glioblastoma patients GTAC has deferred a decision pending the supply of additional information. The second for breast/metastatic liver cancer patients, a decision has yet to be reached;

(ii) a third protocol, from the ONYX/Beatson team proposes to apply a strategy similar to that used in their head and neck cancer trial (see 1.19) to recurrent ovarian carcinoma;

(iii) a fourth protocol proposes to investigate the therapeutic benefits of an adenoviral vector carrying the p53 tumour suppressor gene in a patient group presenting malignant ascites due to gastro-intestinal cancers;

(iv) the final protocol uses an *immuno-modulation* approach using a recombinant *vaccinia virus* administered to patients with metastatic or recurrent breast cancer.

GENERAL COMMENTS ON PROTOCOLS

1.34 The proposals submitted reflect a growing trend, already apparent in the 1994[3] and 1995[4] annual reports towards the use of gene therapy as a new approach to treat cancer. In 1996, the approach was on tumour cell *lysis* rather than immuno-modulation.

1.35 Cystic fibrosis retained its status as the most investigated single gene disorder. Drawing on their initial experience, investigators have incorporated in their subsequent proposals a variety of new approaches to overcome clinical and biotechnological problems.

1.36 All proposers are to be complimented on the way that they have responded to the requests for additional information. The Committee is grateful to proposers for their patience in answering the wide range of questions posed during the review process.

1.37 GTAC will continue to seek advice as appropriate from expert advisers prior to consideration of protocols. It will consider widening the panel of experts as appropriate. The Committee wishes to record its thanks to the expert assessors for their invaluable and constructive contribution to the work of GTAC.

1.38 Dates for GTAC meetings during 1997 are:

12 March

18 June

24 September

10 December

SECTION 2 - REPORT BACK ON GENE THERAPY RESEARCH TRIALS

2.1 Of the 18 gene therapy research protocols approved by GTAC or by its predecessor, the Clothier Committee, up to January 1997, 13 studies have been carried out. A total of 134 patients have been recruited (see Annex 4). No major adverse events have been reported to date. GTAC hopes to receive further detailed reports on some of these trials during 1997.

2.2 Of the remaining five protocols for which approval was given, the availability of vectors, recruitment of suitable patients and/or departmental restructuring have delayed the start of clinical trials.

SECTION 3 - GENE THERAPY : REGULATORY ISSUES

3.1 UPDATE ON GENETICALLY MODIFIED ORGANISMS (GMOs) DIRECTIVES

Directive 90/219/EEC on the Contained Use of Genetically Modified Micro-organisms (GMMs) and 90/220/EEC on the Deliberate Release into the Environment of Genetically Modified Organisms were introduced in order to harmonize GMO legislation between Member States of the then European Economic Community. Adopted in 1990 by the Council and implemented in the UK in 1992 by national regulations they are of particular significance to gene therapy.

The Contained Use Regulations cover the culture, storage, use, transport, destruction and disposal of GMOs where physical barriers limit contact with the environment, whilst the Deliberate Release Regulations are aimed at protecting the environment from any adverse effects from releases of GMOs, and at harmonizing the marketing. A revised Directive on Contained Use is currently being negotiated. One of its main aims is to streamline notification requirements for premises planning to undertake genetic modification activities, in line with a more risk-based system of classification of GMMs. The Commission has recently reviewed the operation of the Deliberate Release Directive and has made recommendations for improvement.

3.2 EC DRAFT DIRECTIVE ON PATENTING - LEGAL PROTECTION OF BIOTECHNOLOGICAL INVENTIONS

A fair and robust patent system is seen as a way to encourage investment in research and development of products. The current system in Europe for patenting of biotechnological products is subject to delay and backlog due to uncertainty over interpretation of the European Patent Convention, for example, in the area of patenting human genetic material, and is subject to national laws. The proposed Directive aims to harmonize patent laws and clarify interpretation underpinning the confidence of industry. It has been re-drafted following the fall of a previous proposal and is currently in the EC negotiation machinery.

3.3 EC DATA PROTECTION DIRECTIVE

The EC Directive on Data Protection is of importance to both clinicians and patients. The Directive was adopted in 1995, and its main provisions must be implemented by October 1998. In March 1996 the Home Office consulted on implementation in the UK. The Government has announced that legislation will be introduced to give effect to the Directive. The Directive is a single market measure aimed at enabling personal data to flow between Member States and offering the individual similar levels of protection throughout the Community. It applies to health and personal social service data even though the exchange of such data between Member States is minimal. One of the Directive s main purposes is to safeguard the fundamental rights of individuals.

3.4 ORPHAN DRUGS - EC DRAFT LEGISLATIVE PROPOSAL

Orphan medicinal products are those which may be developed for the prevention, diagnosis and treatment of rare diseases. The European Commission is expected to adopt a draft legislative proposal on orphan drugs shortly. It is understood that the draft may propose incentives for the pharmaceutical industry to undertake research and development of these products, possibly including a licensing fee waiver, a period of market exclusivity and access to EC research funds. A period of consultation will follow the Commission s adoption of a proposal.

3.5 DRAFT EC DIRECTIVE ON GOOD CLINICAL PRACTICE IN CLINICAL TRIALS

The Commission has recently brought forward proposals for a Directive on Good Clinical Practice in the Conduct of Clinical Trials. It is being fully discussed with Member States, and there was a public consultation in the autumn. The latest draft, which is about to be referred to the Council is now broadly in line with current UK practices and will be supported by a number of guidelines. As the procedures in Member States often differ significantly, the guidelines will mainly, for each area covered, draw together in a single document a summary of individual Member States requirements. This should provide a comprehensive guide to organisations wishing to make multi-national clinical trial applications. The Directive may take up to 18 months to become law, with possibly a further year for implementation by Member States.

SECTION 4 - INTERNATIONAL DEVELOPMENTS

4.1 RECOMBINANT DNA ADVISORY COMMITTEE (US)

The much publicised proposal to withdraw protocol review from the National Institutes of Health s (NIH) Recombinant DNA Advisory Committee (RAC) failed to materialise[7]. The reprieve announced by the NIH in November 1996 followed outline proposals to abolish the 22 year old Committee made earlier that year[8]. The abolition of RAC had been perceived by many as premature, however, a perception that implementation of gene therapy techniques into clinical practice was being hampered by over regulation may have led NIH to have considered this course of action. A smaller RAC with new terms of reference is expected to begin work in 1997.

4.2 VARMUS REPORT

The NIH funds somatic gene therapy to the level of $200 million a year. At the beginning of 1995, the NIH s Director, Harold Varmus chose 14 experts to assess the status and the promise of gene therapy in the US. He asked the *ad hoc* committee to make recommendations regarding the future of NIH sponsored gene therapy research. In December 1995 the co-chairs of the committee, Arno Motulsky and Stuart Orkin published their report[9]. The report concluded that while the expectations and the promise of gene therapy are great, the clinical efficacy has not been definitively demonstrated and in effect gene therapists and their sponsors were overselling the technology. The panel made eight recommendations including calls for more fundamental research into disease *physiopathology* and gene therapy vectors.

4.3 ORGANISATION FOR ECONOMIC COOPERATION AND DEVELOPMENT (OECD)

The need for more fundamental research was elaborated in two recent OECD initiatives:

(i) an OECD report[10] issued in June 1996 following a 1995 Ottawa Workshop on gene delivery systems; and

(ii) a Conference in Rome in December 1996 aimed at exploring novel systems for studying human pathologies.

4.4 BIOETHICS

Shared technology has often led to the globalisation of certain values. It seems appropriate therefore that in the field of human genetics, countries should work together towards the recognition of common ethical frameworks. It is within this context that:

(i) UNESCO is preparing a declaration on the human genome[11];

(ii) the International Bar Association is preparing a convention on genetics which it hopes to have approved by the United Nations General Assembly[12];

(iii) the Council of Europe adopted the Convention on Human Rights and Biomedicine in November 1996 and has agreed that protocols on genetics, medical research, organ transplantation and the protection of the embryo and fetus will be developed under the Convention. The Convention includes a moratorium, for a minimum of five years, on *germ line gene therapy* in humans.

4.5 A EUROPEAN HOME PAGE FOR GENE THERAPY[13]

1996 saw the launch by the European Working Group on Human Gene Transfer and Therapy (EWGT) of an initiative to place essentially european gene therapy information on the World Wide Web on the EWGT home page. The EWGT newsletter is available on this site, however, for commercial reasons access to certain clinical trial and scientific correspondence is limited.

SECTION 5 - OTHER ACTIVITIES: GTAC WORKSHOP

5.1 GENE THERAPY - MYTH AND REALITY: HYPE AND PRACTICALITY

During 1996 GTAC decided to organise the first GTAC Workshop. The Committee considered that it was important to discuss the broader issues concerning somatic gene therapy in humans; what had been achieved over the first 6 years of gene therapy; what might be achievable over the next similar period; and what are the potential barriers to development.

SECTION 6 - REFERENCES

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2 **Gene Therapy Advisory Committee**: Guidance on Making Proposals to Conduct Gene Therapy Research on Human Subjects. Department of Health. London. September 1994.

3 **Gene Therapy Advisory Committee:** First Annual Report November 1993-December 1994. Health Departments of the United Kingdom. London. Department of Health. March 1995.

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5 **Commission of the European Communities**: Council Directive on the contained use of genetically modified micro-organisms. (90/219/EEC). (1990) Offic. J. Europ. Commun., **L117**, 1-14

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7 **Department of Health and Human Services, National Institutes of Health, Recombinant DNA Research**: Notice of intent to propose amendments to NIH guidelines for research involving recombinant DNA molecules. US Federal Register Billing code (61 FR 35774).

8 **Wadman M:** Gene Panel reprieved after public outcry. Nature, 384, 297 (1996).

9 **Orkin S and Motulsky A:** A Report and recommendations of the panel to assess the NIH investment in research on gene therapy 1996*.

10 **Organisation of Economic Cooperation and Development**: Gene Delivery Systems - A State-of-the-Art Review. OECD Publications. France. 1996.

11 **UNESCO: International Bioethics Committee.** Elaboration of a declaration on the Human Genome. UNESCO: Paris (December 1996).

12 **International Bar Association Bioethics Subcommittee of the Law and Medicine Committee**: Draft International Convention on the Human Genome. October 1996.

13 **European Working Group on Human Gene Transfer and Therapy (EWGT) Newsletter No.7. November 1996.**

* found on internet site
http://www.nih.gov/news/panelrep.html

SECTION 7 - GLOSSARY

Ascites

An abnormal accumulation of fluid in the abdominal cavity.

ADA deficiency

In this inherited disease, due to a faulty gene there is a lack of the gene product, the *enzyme* adenosine deaminase, which results in failure of cells to function.

B cell

A type of white blood cell, important in immunity.

Body cell (somatic cell)

The non-germ line cells of the body. Genetic change in these body cells affect only the individual not individuals of succeeding generations.

Cationic lipid (see liposome)

Cell (see also: body cell, germ line cell, somatic cell)

The smallest unit of living organisms which, given the right conditions, can survive independently and reproduce itself. It has been estimated that the body of a human adult comprises 50 million million cells.

Chromosomes

Microscopically dark staining bodies which carry the nuclear DNA, and are the vehicles which carry the DNA during reproduction. Each chromosome contains a very long double strand of DNA, bearing thousands of genes in a linear array. Chromosomes are present in pairs in body cells, but only one of each pair is present in germ line cells. In humans there are normally 46 chromosomes; 44 are arranged and numbered in order of decreasing size, as 22 matching pairs (autosomes). The two remaining chromosomes are sex chromosomes, in females XX and in males XY.

Coding, codes

Refers to stretches of DNA which contain genetic information to produce a protein product.

Cystic Fibrosis Transmembrane Conductance Regulator (CFTR)

The protein plays an essential role in controlling the passage of salts in and out of cells. In cystic fibrosis the gene producing this protein (the CFTR gene) is faulty (mutated).

Cytopathic

The property of an agent, particularly a virus to injure a living cell.

DNA (deoxyribonucleic acid)

The chemical substance in chromosomes and genes in which genetic information is coded.

Electrophysiological, Electrophysiology

The branch of science which deals with body processes and their relation to electrical phenomena. In cystic fibrosis the abnormal CFTR leads to defective chloride and sodium salt regulation and alterations of the cell s electrophysiological activity. In gene therapy evaluation of the activity of these salts is a measure of CFTR correction.

Enzyme

A protein which acts as a catalyst in the body s many chemical reactions. A deficit in the production of an enzyme or its function may result in an inherited disorder of *metabolism*.

Expression (see gene expression)

Fibroblasts

Cells which produce collagen, a major constituent of the connective tissues.

Gene

A part of the DNA molecule of a chromosome which directs the synthesis of a protein.

Genotype

The genetic constitution of an organism.

Gene expression

The production by a cell of the protein for which the specific gene codes.

Gene therapy

Used without qualification means the genetic modification of body cells of an individual patient, directed to alleviating disease in that patient.

Genetic diseases or disorders

Afflictions which are due to defects in the genetic endowment of an individual. They may be the direct consequences of defects in single genes; or in whole chromosomes, parts of which may be lost, duplicated or misplaced; or due to the interaction of multiple genes and external factors in fetal development. Later in life such interactions appear to be the basis of many of the common serious disorders, such as heart disease, diabetes and cancer.

Genetic test

A test, based on DNA research that can be used for diagnostic or presymptomatic testing.

Germ line cells

The cells of the body which transmit genetic information to the next generation. They are the sperm in males and ova in females.

Germ line gene therapy

Gene therapy which seeks to introduce or modify genes in germ line cells. The effect of such a modification would be transmissible to descendants.

Immuno-modulation

Modifying the body s immune response eg. recruiting of *lymphocytes* to recognise cancer cells.

Immune response

A specific white blood cell or antibody response to foreign protein.

Liposome

A fatty droplet containing DNA which can enter a cell, carrying the genes needed for gene therapy.

Lymphocyte

A type of white blood cell, important in immunity.

Lysis, lytic, lyse

The disruption or dissolution of cells or cellular material by chemicals, physical agents, enzymes or some micro-organisms.

Metabolism

Describes the chemical reactions taking place within the body. These reactions are necessary for its maintenance and growth.

Metastatic, metastases

Disease, usually cancer, that has spread from one site to another unconnected organ.

Molecular biology

The study of proteins and *nucleic acids*, substances that make up the living world, their structures and their relationship to biochemical activity; and the substances that are the repositories of genetic information and the agencies for its communication from one generation to the next.

Mutation, mutant

A molecular change in which DNA is altered with genetic consequences. A gene which has undergone mutation is called a mutant; so also is an organism in which the mutant gene is expressed.

Neomycin (neo)

An antibiotic which can be used as a label for gene transfer.

Nucleic acid

DNA is a type of nucleic acid. A more specialised type of nucleic acid is called RNA which is the genetic material of some viruses such as *retroviruses*.

Neural, Neurological

Characterised by or pertaining to nerve cells.

Palliative Treatment

Treatment whose principle aim is to lessen the discomfort the patient may experience during illness.

Plasmid

A small piece of DNA, usually of bacterial origin, capable of reproducing in bacterial cells and carrying genes. Plasmids are used in some gene therapy trials in place of virus vectors or liposomes.

Prophylaxis

Methods of preventing disease or preventive treatment.

Proliferative diseases, Proliferation

Diseases caused by the deregulated multiplication of cells within the body.

Promoter

A DNA sequence which controls genes. Alterations in the promoter may alter the level of gene expression.

Protein

Proteins are essential constituents of the body. They form the structural materials of muscles, tissues, organs and are regulators of function, as enzymes and some hormones. Proteins are coded for by DNA.

Physiopathology

The physiological interpretation or study of disease phenomena.

Recombinant DNA

Using modern scientific techniques it is possible to make alterations to DNA in the laboratory. Genes can be removed, relocated or added, changing the sequence of genes. Such modified DNA is called recombinant.

Retrovirus

A type of virus often used in gene therapy as a vector. Such viruses are usually animal viruses rather than agents of human disease. They are made safe so that they can enter a human cell carrying a gene for gene therapy without causing disease.

Simian Virus

This group of viruses can cause asymptomatic lymphocyte infection in apes and monkeys.

Somatic cell (see body cell)

Stem cell

A cell that throughout life is able to produce all the cells of a particular lineage within an organism. A change, whether accidental or engineered, in the genetic complement of a stem cell will be passed to and expressed in its progeny. Appropriate stem cells are therefore an obvious target in somatic cell gene therapy.

Stereotactic

A method or a description of a method for precisely locating structures in the brain during life.

Suicide genes

In the presence of certain drugs, the protein products of these genes will cause the destruction of the cell carrying the expressed suicide gene.

Transfection, Transfected

Describes the entry and expression in a cell of the gene product carried by the vector.

Tumourigenicity, Tumourigenesis

A process describing the origin or development of tumours.

Tumour suppressor genes

The protein product of a gene that regulates the multiplication of cells. The absence or dysfunction of a tumour suppressor gene is associated with the production of cancer cells.

Vaccinia virus

This is a vaccine strain of virus. Live vaccinia virus has been used extensively in smallpox eradication programmes.

Vectors

In most situations, a new gene cannot be added to human cells without being transported into the cell in some form of a carrier (vector) - usually a virus, a liposome or a plasmid.

Virulence

The capacity of an organism to produce disease.

Virus

A tiny infectious organism, too small to reproduce outside a host cell. Viruses carry nucleic acid surrounded by protein. Some viruses cause disease, eg chicken pox, influenza; others however, suitably modified, can be used as a means of delivering genes into cells.

ANNEX 1 - TERMS OF REFERENCE OF GTAC

The terms of reference of the Gene Therapy Advisory Committee (GTAC) are:

(1) to consider and advise on the acceptability of proposals for gene therapy research on human subjects, on ethical grounds, taking account of the scientific merits of the proposals and the potential benefits and risks;

(2) to work with other agencies which have responsibilities in this field including local research ethics committees and agencies which have statutory responsibilities - the Medicines Control Agency, the Health and Safety Executive, and the Department of the Environment;

(3) to provide advice to UK Health Ministers on developments in gene therapy research and their implications.

The Committee will have a responsibility for:

(a) providing advice for applicants on:

(i) the content of proposals, including the details of protocols, for gene therapy research on human subjects;

(ii) the design and conduct of the research;

(iii) the facilities necessary for the proper conduct of the research;

(iv) the arrangements necessary for long term surveillance and follow up.

(b) Receiving proposals from doctors who wish to conduct gene therapy research on human subjects, and making an assessment of:

(i) the clinical status of the subjects;

(ii) the scientific quality of the proposal;

(iii) the scientific requirements and technical competence necessary, for carrying out gene therapy research effectively and safely;

(iv) whether the clinical course of the particular disorder is known sufficiently well for:

- sound information, counselling and advice to be given to the subject (or those acting on behalf of the subject);
- the outcomes of therapy to be assessable;

(v) the potential benefits and risks for the subject of what is proposed.

ANNEX 2 - MEMBERSHIP OF GTAC

Chairman

Professor Norman C Nevin BSc, MD, FFPHM, FRCPath, FRCP Ed, FRCP
Department of Medical Genetics
Belfast City Hospital

Members

Dr Elizabeth Anionwu PhD, RGN, HV Tutor
Senior Lecturer in Community Genetic Counselling
Mothercare Unit of Clinical Genetics and Fetal Medicine
Institute of Child Health
London

Mrs Rosemary Barnes
Chief Executive
Cystic Fibrosis Trust
Kent

Professor J Burn MD, FRCP**
Northern Genetics Service
Royal Victoria Infirmary
Newcastle

Professor Anthony Dayan MD, FRCP, FRCPath, FFPM, FIBiol
Department of Toxicology St. Bartholomews & The Royal London School of Medicine & Dentistry
London

Reverend Dr Keith Denison MA, PhD
The Church in Wales
Diocese of Monmouth

Dr Brenda Gibson FRCP, FRCPath, DFM
Department of Haematology
Hospital for Sick Children
Glasgow

Professor Ian Hart BVSC, MRCVS, PhD, FRCPath*
UMDS
St Thomas Hospital
London

Mrs Ann Hunt*
Tuberous Sclerosis Association

Professor Theresa Marteau MSc, PhD, CPsychol
Psychology & Genetics Research Group
Guy s Campus
London

Professor James Neil BSc, PhD, FRSE*
Department of Veterinary Pathology
University of Glasgow Veterinary School

Professor Anthony Pinching DPhil, FRCP**
Department of Immunology - Smithfield
St Bartholomews and The Royal London School of Medicine & Dentistry
Queen Mary & Westfield College
London

Miss Eleanor Platt QC
The Temple
London

Sir Brian Richards CBE, BSc, PhD
Peptide Therapeutics Group
Cambridge

Professor C Michael Steel MB, ChB, PhD, DSc, FRCP Ed, MRCPath
School of Biological & Medical Sciences
University of St Andrews

Mrs Irene Train RGN, RM, RHV, QIDN**
Formerly Director Public Health Nursing
Clwyd Health Authority

* Appointed January 1996
** Appointed January 1997

Members Retiring in 1996

Baroness Lloyd of Highbury DBE, MD, FRCP
Formerly Professor of Child Health
Institute of Child Health
London

Professor Derek Crowther PhD, MB, BChir, MA, MSc, FRCP, FRCR
Christie CRC Research Centre
London

Mrs Rosemary M Knights RGN, OND, DN
Warrington Hospital
Cheshire

Professor Peter Lachmann FRCP, FRCPath, FRS
Molecular Immunopathology Unit
Cambridge

Observers

Dr E Gadd
Department of Health
London

Dr Amanda Goldin
Human Genetics Advisory Commission
Office of Science and Technology

Dr Brian Davis MRCP
Medicines Control Agency
London

Dr Lincoln Tsang
Medicines Control Agency
London

Observers retiring in 1996

Dr John Modle
Department of Health
London

Secretariat

Mr Anthony J Taylor
Dr Veronica Lecomte
Mrs Margaret Straughan
Mr Mark Noterman

ANNEX 3 - EXTERNAL EXPERT ADVISERS TO GTAC

During the period of this third report, GTAC sought the views of the following expert advisers during the review of protocols submitted to the Committee.

Dr John Arrand,
Paterson Institute for Cancer Research,
Manchester

Professor John Dodge,
Queen's University of Belfast,
Belfast

Professor Robert Souhami,
Middlesex Hospital,
London

Professor Robin Weiss,
Institute of Cancer Research,
Chester Beatty Laboratories,
London

Professor Anthony Minson,
Division of Virology, Cambridge University,
Cambridge

Professor Don Jeffries,
Dept. of Virology, St. Bartholomew's & Royal
London School of Medicine & Dentistry

Professor Pedro Lowenstein,
Dept. of Medicine, University of Manchester,
Manchester

#	Details	Outline	Outline Approval	Trial Commenced	Vector/ gene	Packaging cell line	No. of Patients
001	SCID-ADA	Institute of Child Health/ Great Ormond Street Hosp	1-93	3-93	pLGAL	pOAM-P1	1
002	CF Nasal trial	Royal Brompton Hosp	3-93	9-93	Liposome DC-Chol/CFTR	—	15
003	B-cell lymphoma	Addenbrookes Hospital/ Royal Bournemouth Hosp	7-93	11-94	pVAC1/anti idiotype immunoglobulin	—	6
004	Neuroblastoma	ICRF Bristol	2-94	—	LNL-6/neo G1N-neo	PA317	—
005	Metastatic melanoma	ICRF Oxford	5-94	6-95	pNASSB-BGal pNASSB-IL2	—	10
006	Metastatic melanoma	Institute of Cancer Research/ Royal Marsden Hosp	2-94	10-94	MFG-S-IL2	GP+env AM12	12
007	CF Nasal trial	Oxford/Cambridge	2-94	5-95	Liposome DC-Chol/CFTR	—	12
008	CF Nasal trial	Edinburgh	5-94	6-95	Liposome DOTAP-CFTR	—	16
009	CF lung trial	Royal Brompton Hosp	9-94	—	Liposome DC-Chol/CFTR	—	—
010	Lymphoma	University College London Medical School	12-94	10-95	pHaMDR-1	AM12M1	3
011	Breast Cancer	Hamersmith Hospital	10-95	1-96	pERCY	—	4
012	Cervical Cancer *	University of Wales, Cardiff	6-95	9-95	TA-HPV	CR2C9	8
013	Hurler s Syndrome	Royal Manchester Children s Hospital Manchester	12-95	—	pLX	GP+env AM12	—

* Investigators have received approval (5/96) to use the same vector in an amended protool

#	Details	Outline	Outline Approval	Trial Commenced	Vector gene	Packaging cell line	No. of Patients
014	Head and Neck Cancer	Beatson Oncology Centre Glasgow	1-96	4-96	Onyx-015	Human embryonic Kidney cell line 293	19
015	CF Nasal trial	Oxford/Cambridge/Leeds/ Manchester Consortium	5-96	7-96	Liposome DC-Chol/CFTR	—	11
016	Head and Neck Cancer	Institute of Cancer Research/ Royal Marsden Hospital	9-96	12-96	SCH58500	Human embryonic Kidney cell line 293	16
017	CF Lung and Nasal Trial	Royal Brompton Hospital	11-96	11-96	pCF1-CFTR#67	—	12
018	Glioblastoma	Beatson Oncology	12-96	—	HSV1 ICP 34.5-1716	BHK 21/C13	—

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